A Review of Antibiotic Use in Pregnancy

By

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Introduction

- Antibiotics account for nearly 80% of all prescription medications during pregnancy
- 20–25% of women will receive an antibiotic during pregnancy.
- Untreated infections such as UTIs or STIs are associated with significant fetal risk including spontaneous abortion, prematurity, and LBW.

- Only 10% of medications marketed since 1980 have sufficient data regarding infantile risk in pregnancy
- Prenatal exposure of the infant to antimicrobials (via self-reporting by the mother) resulted in a lower birth weight of approximately 138 g
- Antimicrobial exposure during pregnancy has recently been linked to childhood obesity
- Prenatal antibiotic risk associated with asthma and wheezing was significant when antibiotics were used in the second to third trimesters but not during the first.

Physiologic changes during pregnancy

- Pregnancy
  - ✓having a developing fetus in the body
  - ✓lasts 280 days or 40 weeks from LNMP
  - ✓causes complex physiologic changes,

including;

- o Endocrine
- o Renal
- o Gastrointestinal
- o Skin

- o Genital
- o Cardiovascular
- o Hematologic
- o Pulmonary

Physiologic changes during pregnancy

- Increases in total body water, blood volume (40–50%), and plasma volume (40–50%) contribute to increases in volume of distribution of various antibiotics.
- Renal blood flow increases by 50%, possibly due to vasodilation of afferent and efferent arterioles as a result of increased progesterone. Ser Cr decreases, while GFR increases elimination of renally excreted antibiotics.

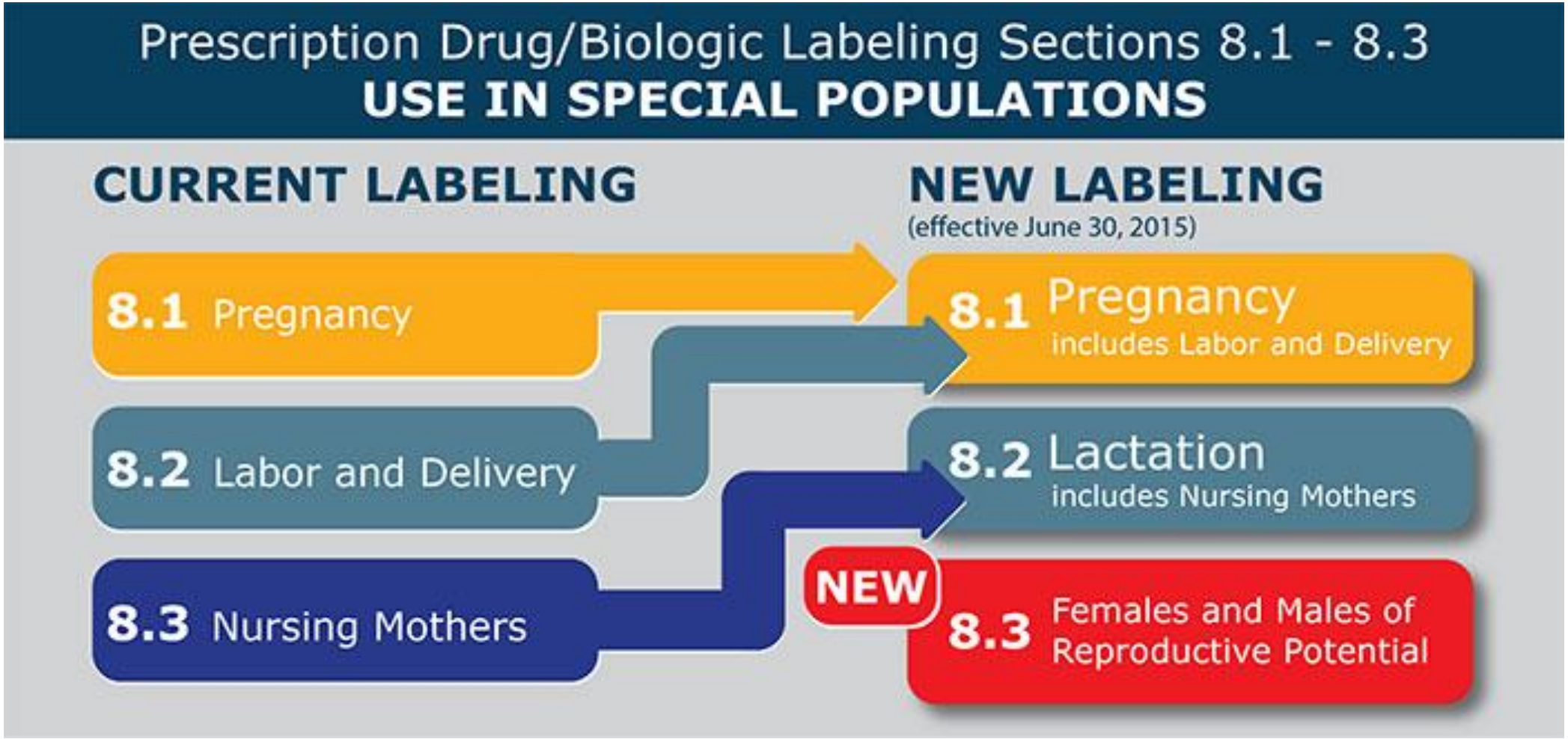
Physiologic changes during pregnancy

- There are known changes in hepatic enzymes during pregnancy, but current data are controversial as to whether these changes lead to clinically significant changes in drug metabolism and subsequent serum concentrations
- Finally, decreases in albumin and alterations in maternal plasma pH are expected to lead to decreased protein binding and increased concentrations of unbound drug

FDA categories

Pregnancy Category Rating	Level of Evidence	Accompanying Text Labeling Requirement
A	No risk in human studies; Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)	None
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women	Because the studies in humans cannot rule out the possibility of harm, [name of drug] should be used during pregnancy only if clearly needed
C	Risk not ruled out; Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks	[Name of drug] should be given to a pregnant woman only if clearly needed
D	Positive evidence of risk; There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks	If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
X	Contraindicated in pregnancy; Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits	[Name of drug] is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

Labeling changes for the new pregnancy and lactation section



The new labeling system

- Specifically, the pregnancy section is divided into “Risk Summary,” “Clinical Consideration,” “Data” (human and animal), and “Pregnancy Exposure Registry” (if applicable)

The new labeling system

- Prescription drugs submitted for FDA approval after June 30, 2015 will use the new format immediately,
- While labeling for prescription drugs approved on or after June 30, 2001 will be phased in gradually.
- Medications approved prior to June 29, 2001 are not subject to the PLLR rule
- The pregnancy letter category must be removed by June 29, 2018

Aminoglycosides

- **Amikacin**, **gentamicin**, **streptomycin**, and **tobramycin** are the most commonly prescribed
- In pregnancy, the serum half-life of aminoglycosides is shorter and clearance is increased. Due to this and a larger volume of distribution in pregnant women, aminoglycosides may have a lower serum peak concentration
- Case reports of irreversible bilateral congenital deafness with maternal use of streptomycin in the first trimester have been described(FDA Category: D)

Aminoglycosides

- Animal studies with gentamicin in rats and rabbits did not result in fetal toxicity.
- Despite toxicity reports, short courses of aminoglycosides may be used in pregnant women with careful monitoring if the likely benefit outweighs the potential risk.
- Possible risks should be explained to the patient, especially in the first trimester.
- Streptomycin use should be avoided.

Beta-Lactams and Related Antibiotics

- **Penicillins**
  - The most widely prescribed antimicrobial class
  - Penicillins generally cross the placenta in high concentrations
  - Due to increased plasma vol and **CrCl** in pregnancy, serum penicillin concentrations may be decreased by as much as 50%, which may require increased doses and/or frequency
  - All penicillins :Cat B.

Beta-Lactams and Related Antibiotics

- **Cephalosporins and Cephamycins**
  - Cephalosporins remain a first-line option for many infections in pregnancy with general use reserved for patients allergic or intolerant to penicillin therapy.
  - Cephalosporins have decreased plasma concentrations in pregnant patients because of increased renal elimination; therefore, potential dosage and frequency increases are required
  - All: Category B

- Potential association between **ceftriaxone** and cardiac malformation:

  (Findings from a Michigan Medicaid database)
- **Ceftriaxone:** drug of choice for the treatment of gonorrhea during pregnancy
- **Ceftriaxone:** potential risk of kernicterus in neonates

Carbapenems

- There is a paucity of data regarding the use of carbapenems during pregnancy
- Ertapenem, meropenem, and doripenem: Category B
- Imipenem-cilastatin: Category C.
- Carbapenem therapy should be reserved for infections that are resistant to penicillin and cephalosporin therapy with limited alternatives

Fluoroquinolones

- Pregnancy Category C
- Generally contraindicated in pregnancy
- Fluoroquinolones may be safe during the first trimester but are not recommended
- There is a suggested association with fluoroquinolones and renal toxicity, cardiac defects, and CNS toxicity in the fetus
- Animal data: bone and cartilage damage in the fetus
- fluoroquinolone use in pregnancy is only recommended if there is no alternative

Glycopeptides and Lipoglycopeptides

- Vancomycin (glycopeptide): Category B
- Eliminated by glomerular filtration in the kidneys, and 55% protein bound, which may lead to alterations in kinetics during pregnancy.
- Crosses the placenta and has been found in umbilical cord
- Because of limited information, caution is warranted during the first trimester
- Telavancin, oritavancin, and dalbavancin should be avoided unless the benefits of treatment outweigh the risk to the fetus

Macrolides and Ketolides

- In a review of maternal erythromycin exposure over 15 years, erythromycin was persistently associated with cardiovascular defects (RR 1.70; 95% CI 1.26–2.39). Most defects were considered mild.
- Any product containing erythromycin should be used with caution in pregnancy and only when benefit outweighs risk.
- Azithromycin: Category B.
- Clarithromycin: Category C.

- Telithromycin(a semi-synthetic erythromycin derivative) is a ketolide antibacterial with similar structure and activity as the macrolides.
- There are no human data for the use of telithromycin in pregnancy, (Category C).
- Given its relative limited utility and potential risks, telithromycin should be avoided in pregnancy.
- D/C in the U.S. in 2016

Oxazolidinones

- Linezolid and tedizolid(Pregnancy Category C)

Tetracyclines

- Labeled as Pregnancy Category D
- Teratogen in humans
- Tetracyclines cross the placenta and when used beyond the 2nd trimester, they can bind to ca++ and cause permanent discoloration of bones and teeth.
- They are contraindicated past the 5th week of pregnancy.
- In rare cases, doxycycline may be considered in pregnant women who have life-threatening tick-borne illnesses.

Clindamycin

- Is a lincosamide antibiotic
- Preg Category B.
- A study of 647 newborns that had been exposed to clindamycin in the first trimester did not support an association between the drug and congenital defects.
- Evidence is lacking for using oral clindamycin late in pregnancy
- Vaginal clindamycin is not recommended due to systemic absorption (up to 30%), increased risk of adverse neonatal outcomes (neonatal infection and low birth weight), and lack of efficacy.
- Guidelines recommend avoiding vaginal clindamycin in the latter half of pregnancy

Daptomycin

- Pregnancy Category B
- Is primarily excreted by the kidneys
- Daptomycin should be used in pregnancy only if the benefit outweighs the risk.

Metronidazole

- Pregnancy Category B
- However It is contraindicated in the first trimester
- Vaginal metronidazole should be used with caution during pregnancy, as a potential link with congenital hydrocephalus has been suggested

Nitrofurantoin

- Pregnancy Category B
- Animals exposed to doses 25 times that of normal human administration did not result in teratogenic effects
- Nitrofurantoin may increase the risk of hemolytic anemia in pregnant patients with severe G6PD deficiency as indicated by one case report
- Nitrofurantoin remains an option for treatment of UTI and prevention of recurrent UTI in pregnant women

Polymyxins

- Polymyxin B and polymyxin E: Pregnancy Category C
- In an animal model examining risk during pregnancy, polymyxin B demonstrated toxic effects to the embryo in a dose-dependent manner
- Due to the limited use in pregnant women and high potential for adverse events, strong caution is advised prior to use.

Sulfamethoxazole-Trimethoprim

- Pregnancy Category C
- Animal studies have demonstrated teratogenic effects.
- Should be avoided in the 1st trimester due to the mechanism of trimethoprim as a folate antagonist. (Neural tube and cardiac defects, cleft palates, limb malformations)
- Maternal folic acid supplementation reduces the risk of major fetal malformations from trimethoprim
- Sulfonamides should not be used in the third trimester as they theoretically result in an increase of unbound bilirubin and risk of kernicterous.

- Co-trimoxazole use during the first trimester has been also associated with a 3-fold increase in urinary tract defects
- Its use during the last two trimesters has been associated with SGA newborns.
- In the 2nd and 3rd trimesters, use should be limited to those situations when the benefits outweigh the potential risks

Antimycobacterial Agents

- A systematic review demonstrated overall safety of first-line therapy comparable to the general population.
- INH: A nonsignificant increase in hepatitis has been observed in pregnant women, particularly in those with preexisting liver disease and HIV.
- INH is also recommended for latent TB infection (LTBI) in pregnancy as a first-line treatment.
- Low-risk patients may be advised to defer treatment of LTBI until after pregnancy
- Vit B6 daily 25–50 mg/day is advised in all pregnant women receiving INH to mitigate neurologic complications in the mother and newborn

Antimycobacterial Agents

- Rifampin: Pregnancy Category C
- Rifampin use in animals at up to 10 times the normal human dose did not produce any fetal abnormalities
- Dose up to 15 times human exposure at the time of conception was associated with significant fetal malformations.
- An association between rifampin and newborn bleeding has been described, so prophylactic vitamin K may be necessary

Antimycobacterial Agents

- Data on alternative rifamycins—rifabutin and rifapentine—are limited in pregnancy and should be used with caution.
- They are considered Pregnancy Category C and not recommended in the current guidelines.

Antimycobacterial Agents

- Ethambutol: Category B (safe)
- It is associated with retrobulbar neuritis in the general population
- Pyrazinamide: (Pregnancy Category C)
- Careful risk assessment is needed and enhanced monitoring, specifically of uric acid and liver enzymes, is suggested

Anti –fungal drugs

- Vulvovaginal candidiasis
- 25% of pregnant women
- not associated with adverse pregnancy outcomes
- Tx is for relief of symptoms

Anti –fungal drugs

- Nystatin cat B
- Clotrimazole cat B
- Miconazole, Butoconazole Terconazole ,Tioconazole : Cat C

- To date no topical antifungal tx was associated with teratognecity
- Griseofluvin- Cat C , its effect on pregnant woman not established

systemic fungal infections

Require larger dose of anti fungals

Systemic antifungal agents - toxic medications

use in pregnancy has been limited to life- threatening fungal infections

Fluconazole-Cat D

Ketoconazole- Cat C

Itraconazole- Cat C

Amphotercin B – Cat B

Flucytocine – Cat C

Anti- helminthic drugs

- Hook worm & other helminthes
- May cause anemia, reduced birth weight and increased perinatal mortality Most drugs are Cat- C, however most of them are OTC
- Lack of information for most of them
- Mebendazole – Cat C
- Albendazole- Cat C
- Ivermectin •Pyrantel Pamoate- Cat C
- Praziquantel Cat B

- Cutaneous Leshmaniasis

  no significant risk for mother or fetus

  treatment delayed till delivery

  Treatment same as non pregnant woman